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| EXAMINER |
|---|
| EPPERSON, JON D |

| ART UNIT | PAPER NUMBER |
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| 1639 | 18 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| | Application No. | Applicant(s) | |
|---|---|---|---|
| **Office Action Summary** | 09/661,927 | DOWER ET AL. | |
| | **Examiner** | **Art Unit** | |
| | Jon D Epperson | 1639 | |

File Copy

*-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-137* is/are pending in the application.

4a) Of the above claim(s) *1(in part),4-13,17-24,36,38-39,41-45, 51,55,57,59-65,67,69-137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,14-16,25-35,37,40-50,52-54,56,58,66 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## DETAILED ACTION

### *Status of the Application*

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on May 1, 2003 (Paper No. 17).

### *Priority Claims*

2. The priority filing date of September 14, 1999 for application 60/154,071 is acknowledged.

### *Status of the Claims*

3. Claims 1-137 are pending in the present application.

4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 17 is acknowledged (Applicants elected Group II, claims 1 (in part), 2-40 and 46-68) and claims 1 (in part), 41-45 and 69-137 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

5. Please note: Applicant's elected species (glycocholic acid, hydrolase, transformed cell population, exogenous, bile acid transporter) was found in the art. Furthermore, Applicant's

*specifically* elected species (6-hydroxy hexanoic acid, Luciferin, CZ15-73, reaction in single vessel as in claim 35, luciferase) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

6. Claims 4-13, 17-24, 36, 38-39, 51, 55, 57, 59-65 and 67 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 6 (see below i.e., ***Response to Restriction and/or Election of Species***).

7. Therefore, claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are examined on the merits in this action.

## *Response to Restriction and/or Election of Species*

8. Applicant's election of Group I (claims 1 (in part), 2-40 and 46-68) in Paper No. 17 with traverse is acknowledged.

9. The traversal is on the ground(s) that **[1]** restriction within a claim is improper (e.g., see Paper No. 17, pages 2-3; see also Paper No. 11, pages 1-3), **[2]** there is no search burden because the claims overlap in scope i.e., the searches would be mostly coextensive (e.g., see Paper No. 17, page 3, last paragraph; see also Paper No. 11, page 3, paragraph 3), **[3]** there is no search burden because Groups I-III are classified in the same classifications (see Paper No. 11, page 3, paragraph 3), **[4]** there is no search burden between Groups I-V (now referring to Paper No. 7 wherein Group I refers to claims 1-68) because the Groups are related and have been classified in the same class and subclass and, as a result, a single search of all claims can be made without burden (see paper No. 7, pages 3-4).

10. These arguments were fully considered but were not found persuasive. The Examiner contends **[1]** that Applicants cited case law does not apply here because Applicants claims are drawn to an <u>improper</u> Markush whereas the case law cited by Applicants is applied only to <u>proper</u> Markush claims. However, even if *assuming arguendo* that Applicants case law does apply here, the Examiner contends that Applicants claims are still properly restricted because their "Markush" listing of transport proteins and ligands <u>lack unity</u>. According to MPEP § 803.02,

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, ***<u>unless the subject matter in a claim lacks unity of invention</u>***. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Here, Applicants claims lack unity of invention because (1) they do not share a common utility (e.g., the carrier-type transport protein to which a particular ligand is to be screened has not been specified) **and** (2) they do not share a substantial structural feature disclosed as being essential to that utility (even if a particular carrier-type transport protein were specified by Applicants they have not disclosed any "core structure" that is essential for this binding). Consequently, the Examiner contends that restriction is proper because Applicants claims lack unity of invention as outlined above in MPEP § 803.02.

Furthermore, the Examiner contends that the "totality of the resulting fragmentary claims" in this case does add up to the full scope of Applicants original claim (i.e., screening the protein + screening the ligand + screening the protein & the ligand, which constitutes Groups I-III is equal to "screening protein and/or ligand", which constitutes the full scope of claim 1) and thus the C.C.P.A. excerpt cited by Applicants (see Paper No. 17) does not apply either.

Finally, contrary to Applicants assertion, the Examiner is not aware of any *per se* rule that prohibits the restriction of a single claim. The Examiner notes that 35 U.S.C. § 121 states that you must restrict between inventions not between claims. Consequently, an Examiner must restrict a single claim when the claim contains more than one patentably distinct invention.

The Examiner also contends **[2, 4]** that while there may be overlapping subject material between the Groups the searches would not be coextensive because there is also non-overlapping subject material and, as a result, the searches would not be coextensive (see original restriction disclosing non-overlapping subject matter).

The Examiner's position is that **[3-4]** the inventions do not have to fall within different classifications in order to be considered patentably distinct. See MPEP § 817(D)(3-5). The

Examiner can require restriction even when the inventions fall within the same classification provided that the claimed inventions represent divergent subject matter, divergent fields of search or show that search terms for one groups are not required for the other.

Because these inventions are distinct for the reasons of record and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Furthermore, the claimed subject matter could also be classified into many different classifications. There are just too many different classifications to list here so the Examiner picked one; however, this does not mean that the Groups would necessarily fall within the same classification. For example, claim 1 could be classified in any of the following classes and subclasses e.g., class 435, subclass 6, 7.1, 320.1, 455; DIG 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21; class 436, subclass 501, 63; class 536, subclass 23.1 depending on the types of materials being screened i.e., the nature of the ligands and the types of methods being used to screen said ligands, which suggests that if anything Applicants claims should be further restricted to a specific class of proteins, ligands and cell populations.

11. Applicant's election of species (e.g., esterase, ester cleavage site, luciferase, methods conducted within a single reaction vessel, transformed cell population, exogenous source) in Paper No. 17 without traverse is also acknowledged.

12. Applicant's election of species (e.g., glycocholic acid, 6-hydroxyhexanoic acid, Luciferin, CZ15-73, ileal bile acid transporter, signal detection approach as described in claim

14) in Paper No. 14 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

13. Applicant's election of species (e.g., CHO cells) in Paper No. 11 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

14. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

***Information Disclosure Statement***

15. The information disclosure statement filed March 19, 2001 (Paper No. 4), fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because two publications cited therein, marked AN and AO, lack publication dates, a necessary element for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these two publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

16. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

17. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

***Specification***

18. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 1 outlines method steps for screening a "ligand" comprising both a "compound" and a "reporter" that binds to a "carrier-type transport protein" wherein a "populations of cells" expresses said transport protein. The scope of this claim includes an infinite number of methods for producing an infinite number of structural variants (e.g., an infinite number of ligands, an infinite number of compounds, an infinite number of reporters, an infinite number of carrier-type transport proteins) wherein no distinguishing structural attributes are provided for the members of the ligands, compounds, reporters and carrier-type transport proteins. For example, the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "compounds" or "reporters" that comprise the ligands. Although the specification discloses many possible "ligands" and "carrier-proteins" that "might" be used (e.g., see Specification, pages 9-10; see also 35 USC 102 rejections below), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these ligands, compounds, reporters, carrier-proteins share.

Please also note that the "protein" and "ligand" are only defined using functional language e.g., the proteins ability to act as a "carrier" or the ligands ability to bind to a carrier-type transport protein (see also 35 USC 112, second paragraph rejection below). With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. Similarly, the instant claims define the components of the claimed invention only by their functional properties (e.g., "ability to act as a transporter or ability to bind a protein")(emphasis provided). The CAFC held this sort of functional definition insufficient to adequately describe the claimed product.

Consequently, it is not possible to determine *a priori* which ligands, compounds, reporters, carrier-proteins would be encompassed by Applicants' broad claims because there is no common structural attributes that can link together ***all*** of these potential catalysts in either library i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of ligands, compounds, reporters, carrier-proteins that should be included in this genus from the few examples provide by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails

to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like dipeptide transporter, oligopeptide transporter, simple sugar transporter (e.g., see Specification, pages 9-10; see also page 32, last paragraph) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, Applicants' only working examples are generally directed toward the use of either a dipeptide library against a PEPT1 transporter or a glycocholic acid library against a ASBT bile acid transporter library that are known to have broad substrate specificity (see Specification, Examples; see also 35 U.S.C. § 102 rejections below). These examples, however, do not "teach" the enormous and highly variant genus that is currently claimed.

20. Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening a library of dipeptides for a PEPT1 dipeptide transporter or a library of glycocholic acid derivatives for the ASBT ileal bile acid transporter, is not enabling for the vast majority of "ligands", "carrier-type transporter complexes" and "population of cells" wherein the ligand is internalized within the population of cells. This is an enablement rejection.

Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and use the claimed invention. Applicant has not provided enough examples of how to make and use the claimed invention to be enabling for the full breadth of the claims. It is clear from applicants' specification how one might practice this invention with carrier-type transport proteins that show broad substrate specificity (i.e., the PEPT1 and ASBT transporters) and reporters that are stable and do not interfere with the assayed compounds ability to bind and/or be transported by the transport proteins. However, Applicants have not provided sufficient guidance as to how to make/use ***any*** ligands with ***any*** carrier-type transport protein that are internalized within ***any*** population of cells, especially carrier-type transport proteins that do not show broad specificity (see example below).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant claims are broad. They read on an infinite number of methods for screening an infinite number of ligands comprising an infinite number of compounds and an infinite number of reporters against an infinite number of carrier-type transport proteins. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The state of the prior art and the level of predictability in the art is low or absent as exemplified by Abe et al. Abe et al discloses a library of dipeptide "compounds" that are conjugated to a fluorescent "reporter" (i.e., Flu or Coum) that are used as "ligands" for the PEPT1 dipeptide "carrier-type transport protein" (see Abe et al, abstract; see also Materials and Methods section). However, Abe et al clearly shows that although these dipeptide ligands bind to the PEPT1 transporters, the transporters do not "transport" the ligands inside the population of cells and that the reason for this anomaly is not known (see Abe et al, page 30, column 1, paragraph 1, "The reasons that this fluorescent dipeptide [citing other similar dipeptides with different reporter labels that are transported] is transported

and our fluorescent dipeptide is not transported is not known) (emphasis added).

Consequently, the Examiner contends that just because you can show that one ligand will bind to a carrier-type protein and subsequently be internalized within a cell does not mean that ***any*** other ligand will follow suit with ***any*** other transport protein i.e., the nature of the invention is not predictable. Here, Abe et al demonstrates that one of Applicants preferred ligands (i.e., a dipeptide library) will NOT be internalized by one of Applicants preferred carrier-type proteins (e.g., PEPT1) and they say that the reason for this lack of internalization is not known i.e., the art is not predictable even for Applicants preferred embodiments.

Furthermore, Abe et al shows yet another level of unpredictability when they try (and fail) to use (Coum)Lys-Sar and Val-Lys(Coum). Here, the "Coum" label was rapidly degraded inside the cell and, as a result, the researchers were not able to determine the initial uptake of Coum analogous. Consequently, even ligands that are internalized (which often does not happen for no apparent reason, see above) may still not work because their detection labels can be unexpectedly degraded.

(4) The level of one of ordinary skill: The level of skill required for this invention would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of ligands, carrier-type transport proteins and cell types that fall within the scope of these broad claims. Furthermore, there is no generic strategy for **[a]** determining which transport proteins have a limited specificity (and hence will not work) from those that have a

broader specificity (see Abe et al, page 24, column 1, paragraph 1 discussing specificity requirements) **[b]** determining which reporters will prevent the complex from binding to the transport proteins (and hence will not work) from those reporters that permit binding, **[c]** determining which reporters will bind to the transport proteins but nevertheless prevent uptake (and hence will not work, at least for the full scope of Applicants claims which includes internalization) from those that will allow transport (see Abe et al, page 30, column 1, paragraph 1 stating that reporter molecules can at times unexpectedly (i.e., unpredictably) prevent uptake in a cell for no known reason) or **[d]** determining which reporters will be degraded in a particular host cell (and hence will not work) from those that are stable (see Abe et al, page 29, column 2, paragraph 3 showing that some reporters can be unexpectedly degraded by a particular host cell).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed compounds. The Examiner contends that Applicants few examples do not teach the entire genus because the genus is broad and highly variant and because Applicants few working examples cannot be extrapolated to encompass a broader scope because Applicants have provided no generic strategy that would enable such an extrapolation and Abe et al shows that even embodiments that are closely related to Applicants do not work. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use

the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Please note that the Abe et al reference is cited here only to show that Applicants are not enabled for the "full scope" of their claimed invention i.e., the above rejection is a scope rejection, which indicates, that a portion of applicant's invention is indeed enabled by the specification, but points out that a much larger portion of the claimed invention is not enabled. Accordingly, in this respect an enablement rejection for scope is not internally or legally inconsistent with a finding that enabled embodiments are indeed either anticipated or rendered obvious by the prior art (see 35 U.S.C. § 102 rejections below).

***Claims Rejections - 35 U.S.C. 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-3, 14-16, 25-35, 37, 40-50, 52-54, 56, 58, 66 and 68 are rejected because the "carrier-type transport protein" in these claims is not defined with any chemical or physical characteristic, but only by functional properties (i.e., there is no consensus sequence or common structural motifs that would encompasses the full breadth of this term). Furthermore, there is no common structural elements that would link **ALL** of the proteins that have these functional features. Consequently, a person of skill in the art would not readily envision **ALL** of the structures that would fall within the broad scope of this functional language and, as a result, the metes and bounds of the claimed invention cannot be determined.

A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169.

## *Claims Rejections - 35 U.S.C. 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1, 2, 35, 37, 56, 58, 66 and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Abe et al (Abe, H.; Satoh, M.; Miyauchi, S.; Shuto, S.; Matsuda, A.; Kamo, N. "Conjugation of Dipeptide to Fluorescent Dyes Enhances its Affinity for a Dipeptide Transporter (PEPT1) in Human Intenstinal Caco-2 cells" *Bioconjugate Chem.* **December 31, 1998** (on web), *10*, 24-31) (IDS Paper No. 8, Ref. No. 7).

For ***claims 1, 35, 56, 58, 66***, Abe et al (see entire document) discloses a method for screening for fluorescent dipeptide conjugate ligands to the Dipeptide Transporter (PEPT1) protein, which anticipates claim 1. For example, Abe et al discloses **[a]** providing a library comprising different complexes (e.g., Val-Lys or Lys-Sar conjugated to fluorescein isothiocyanate (Flu) or coumarin-3-carboxylic acid (Coum) and [$^{14}$C]Gly-Sar, see page 24, column 2, paragraph 1; see also page 27, "Uptake Experiments in Monolayer Caco-2 Cells" section), each complex comprising a compound (e.g., Val-Lys, Lys-Sar, Gly-Sar) and a reporter (e.g., Flu, Coum, [$^{14}$C]) the compound varying between different complexes (Val-Lys, Lys-Sar, Gly-Sar are not the same). Furthermore, Abe discloses **[b]** providing a population of cells, one or more of which expresses one or more carrier type proteins (see Abe et al, Title disclosing the Dipeptide Transporter (PEPT1) in Human Intestinal Caco-2 Cells). Abe et al also discloses **[c]** contacting the population of cells with a plurality of complexes from the library (see Abe et al, page 30, column 1, paragraph 1, "the fluorescent analogues can bind the binding site of the transporter"; see also Figure 1 showing simultaneous addition of Gly-Sar with Val-Lys(Flu) or (Flu)Lys-

Sar). Finally, Abe et al discloses **[d]** detecting a signal from the reporter of a complex that is bound to a cell or internalized within a cell, the signal providing an indication that a complex whose reporter generated the signal comprises a compound that is a ligand for a carrier-type transport protein (see Abe et al, page 29, column 1, paragraphs 4-6 disclosing both fluorescence detection and detection of radioactivity).

For ***claim 2***, Abe et al discloses both fluorescence and radioactivity within the cell (see Abe et al, page 29, column 1, paragraphs 4-6).

For ***claim 37***, Abe et al discloses different reporters e.g., Flu or Coum and [$^{14}$C].

23. Claims 1-3, 14, 35, 56 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Swaan et al (Swaan, P. W.; Hillgren, K. M.; Szoka, F. C.; Oie, S. "Enhanced Transepithelial Transport of Peptides by Conjugation to Cholic Acid" *Bioconjugate Chem.* **1997**, *8*, 520-525).

For ***claims 1, 35, 56, 66***, Swaan et al (see entire document) discloses screening radiolabeled [$^{3}$H]bile acid-peptide conjugates against a bile acid transporter expressed in CaCo-2 cells, which anticipates claim 1 (see Swaan et al, abstract, figures 1-2 wherein the "compounds" = the different peptides; the "reporter" = [$^{3}$H]bile acid; the "population of cells" = CaCo-2; the "signal" = radioactivity).

For ***claims 2-3, 14***, Swaan et al discloses the enzymatic cleavage via cellular peptidases of the [$^{3}$H]bile acid-peptide conjugate into [$^{3}$H]cholic acid (see Swaan et al, figure 4).

***Claim Rejections - 35 USC § 103***

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 1-3, 14, 35, 56, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swaan et al (Swaan, P. W.; Hillgren, K. M.; Szoka, F. C.; Oie, S. "Enhanced Transepithelial Transport of Peptides by Conjugation to Cholic Acid" *Bioconjugate Chem.* **1997**, *8*, 520-525) and Dawson et al (U.S. Patent No. 5,589,358) (Date of Patent is **December 31, 1996**) (IDS Paper No. 8, Ref. No. 2).

For ***claims 1-3, 14, 35, 56 and 66***, Swaan et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-3, 14, 35, 56 and 66 and, consequently, also renders obvious claims 1-3, 14, 35, 56 and 66.

The prior art teaching of Swaan et al differs from the claimed invention as follows:

For ***claim 68***, the prior art teachings of Swaan et al differs from the claimed invention by not specifically reciting the use of a "control" (see Swaan et al, ).

However, Dawson et al teaches the following limitations that are deficient in Swaan et al:

For ***claim 68***, Dawson et al (see entire document) teaches that cells expressing bile acid transporters can be used in high throughput screening with "controls" (see Dawson et al, column 22, paragraph 2-3).

It would have been obvious to one skilled in the art at the time the invention was made to use the screening method as taught by Swaan et al with the "controls" as taught by Dawson et al because Dawson et al teaches that "controls" are useful for obtaining accurate results. Furthermore, one of ordinary skill in the art would have been motivated to use "controls" so that more accurate measurements could be obtained.

## *Contact Information*

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
July 20, 2003

BENNETT CELSA
PRIMARY EXAMINER